Child's Nervous System (2018) 34:765–770
https://doi.org/10.1007/s00381-017-3675-8

CASE REPORT

Disseminated juvenile xanthogranuloma occurring after treatment of Langerhans cell histiocytosis: a case report

Tae-Kyu Lee[1] · Tae-Young Jung[1] · Hee-Jo Baek[2] · Seul-Kee Kim[3] · Kyung-Hwa Lee[4] · Sook Jung Yun[5]

Received: 7 November 2017 / Accepted: 27 November 2017 / Published online: 5 December 2017

Abstract

Case presentation An 11-year-old boy presented with a complaint of a painful temporal mass. Brain magnetic resonance imaging (MRI) showed a 3-cm-sized, homogeneously enhancing mass in the greater wing of the left sphenoid bone, which was diagnosed as Langerhans cell histiocytosis (LCH). Chemotherapy with vincristine and prednisolone was performed for 1 year. After 1 year and 11 months off treatment, he developed symptoms such as polydipsia and polyuria. Brain MRI showed thickening of the pituitary stalk with enhancement, suggestive of LCH involvement, and no recurrence in the sphenoid bone. After 4 years and 4 months off treatment, he developed multiple, subcutaneous, asymptomatic, and yellowish variable-sized papules on his face, posterior neck, and back, which were pathologically diagnosed as juvenile xanthogranuloma (JXG). Brain MRI revealed multifocal enhancing skull lesions in the left parietal, right frontal, and left occipital bones, which were also diagnosed as JXG. After 5 years and 8 months off treatment, the number of variable-sized skin lesions was increased without changes in the lesions in the skull and pituitary stalk.

Conclusion We report a case of disseminated JXG occurring after treatment of LCH. These clinical co-presentations suggested a close relationship between their pathogenesis.

Keywords Langerhans cell histiocytosis · Juvenile xanthogranuloma · Chemotherapy

✉ Tae-Young Jung
jung-ty@chonnam.ac.kr

✉ Hee-Jo Baek
PE00069@chonnam.ac.kr

[1] Department of Neurosurgery, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, 160, Ilsim-ri, Hwasun-eup, Hwasun-gun, Jeollanam-do 519-809, Republic of Korea

[2] Department of Pediatrics, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, 160, Ilsim-ri, Hwasun-eup, Hwasun-gun, Jeollanam-do 519-809, Republic of Korea

[3] Department of Radiology, Chonnam National University Medical School, Chonnam National University Hospital, Gwangju, Republic of Korea

[4] Department of Pathology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Jeollanam-do, Republic of Korea

[5] Department of Dermatology, Chonnam National University Medical School, Chonnam National University Hwasun Hospital, Jeollanam-do, Republic of Korea

Introduction

Histiocytoses are characterized by the proliferation of histiocytic cells such as dendritic cells or machrophages, and they are classified into Langerhans cell histiocytosis (LCH) and non-LCH and malignant histiocytoses [1–3]. Non-LCH includes juvenile xanthogranuloma (JXG) and related diseases such as xanthoma disseminatum, solitary spindle cell xanthogranuloma, progressive nodular histiocytosis, generalized eruptive histiocytosis, benign cephalic histiocytosis, and Erdheim-Chester disease. Their clinical behaviors vary from mild to life-threatening disseminated disease.

Among them, LCH refers to a group of related disorders characterized by abnormal uncontrolled histiocyte infiltration with ultrastructural or immunophenotypic characteristics of Langerhans cells, which may involve the bones, lungs, liver, skin, hypothalamus, posterior pituitary, and the lymphatic system [1]. JXG is the most common form of non-LCH, and it is a benign disease usually involving skin and/or mucosal surfaces [1]. Occasionally, it may involve a systemic organ. Histologically, JXG appears as

dermal nodules containing foamy cells, giant cells, and Touton cells. Although LCH and JXG are considered as different diseases, a concomitant or metachronous presentation of LCH and JXG has been reported in the same patients [2, 4–8]. These rare cases may suggest the close relationship between JXG and LCH.

Some papers have reported cases of young patients with JXG developing after treatment of LCH [2, 5–8]. The locations of JXG were the skin and throat, and they were mostly localized lesions. In this study, we report a case of a 16-year-old boy who developed JXG with multiple disseminated lesions on the skin and skull 4.5 years after chemotherapy for LCH in the left zygomatic bone.

Case presentation

An 11-year-old boy presented with a complaint of a painful temporal mass. Brain magnetic resonance imaging (MRI) showed a 3-cm-sized, homogeneously enhancing mass in the greater wing of the left sphenoid bone with extracranial extension and dural invasion (Fig. 1a). He underwent biopsy. Pathologically, eosinophils were predominantly observed (Fig. 2a). The tumor cells were immune-positive for S-100 protein and CD1a. LCH was diagnosed. On systemic evaluation, there were no abnormal findings on abdominal ultrasonography, and there was an increased uptake in the sphenoid bone on whole body bone scan (WBBS) (Fig. 1b). Chemotherapy with vincristine and prednisolone was performed for 1 year. After treatment, there was no enhanced mass on the follow-up brain MRI and there was no increased uptake on WBBS (Fig. 1c, d). After 1 year and 11 months off treatment, he developed symptoms such as polydipsia and polyuria. Brain MRI showed thickening of the pituitary stalk with enhancement, suggestive of LCH involvement, and no recurrence in the sphenoid bone (Fig. 3a, b). A diagnosis of central diabetes insipidus was made based on water deprivation test, and desmopressin was prescribed. On a regular radiologic follow-up at 6-month intervals, no abnormal findings were observed in WBBS, brain MRI, and abdominal ultrasonography (US) except for the pituitary stalk lesion. After 4 years and 4 months off treatment, he developed multiple, subcutaneous, asymptomatic, and yellowish variable-sized papules on the face, posterior neck, and back. Biopsy of a

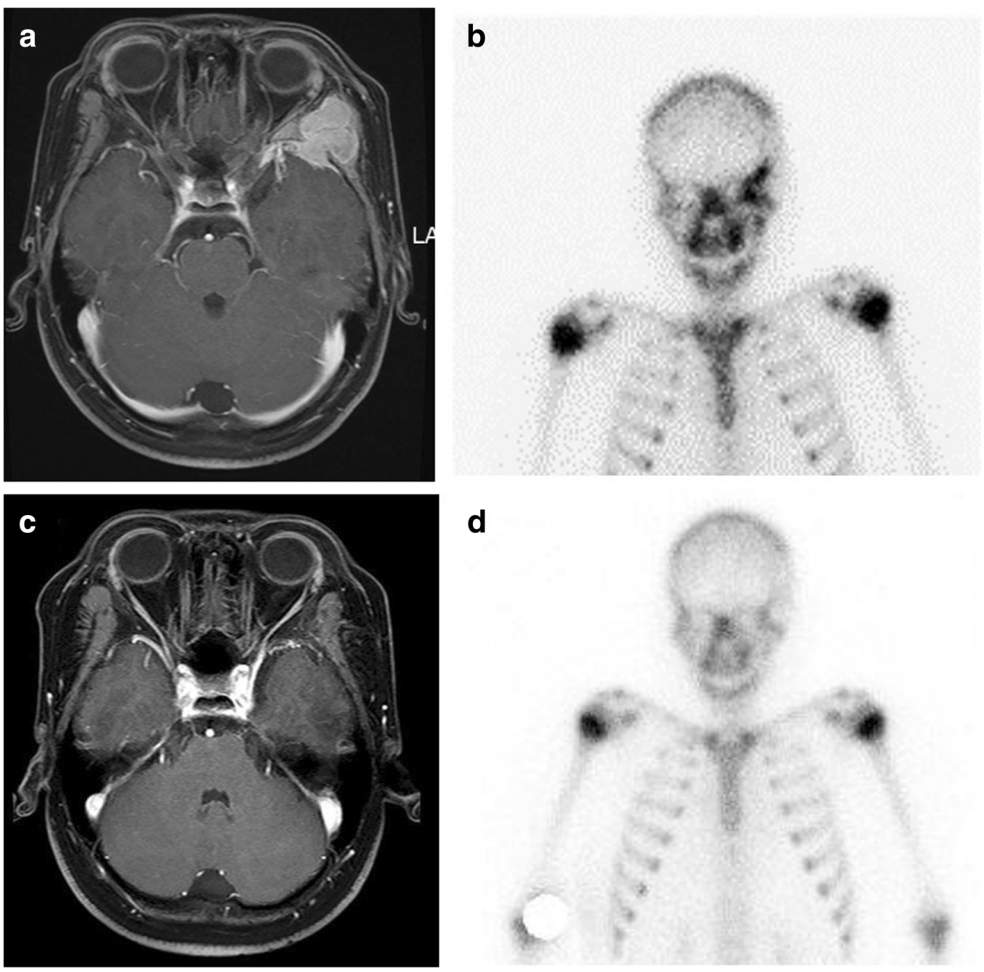

Fig. 1 The radiologic findings of Langerhans cell histiocytosis. **a** Brain magnetic resonance imaging (MRI) showed a 3-cm-sized, homogeneously enhancing mass in the greater wing of the left sphenoid bone with extracranial extension and dural invasion. **b** There was an increased uptake in the sphenoid bone on whole body bone scan. **c** After treatment, there was no enhanced mass on the follow-up brain MRI. **d** There was no increased uptake on WBBS

0.6-cm-sized posterior neck lesion was performed (Fig. 4a). The pathology showed intradermal aggregation of Touton-type giant cells with foamy histiocyte infiltration (Fig. 4b). The tumor cells were immune-positive for CD68 (Fig. 4c), and immuno-negative for S100 and CD1. The skin lesions were diagnosed as JXG. Brain MRI and WBBS examinations revealed multifocal enhancing skull lesions in the left parietal, right frontal, and left occipital bones (Fig. 3c, d), and a persistently thickened pituitary stalk. At follow-up 3 months later, brain MRI showed no change in multiple skull lesions. For the pathological diagnosis of the skull lesion, the left occipital mass was resected and cranioplasty was performed using an artificial bone. The lesion showed focal osteolytic changes with indistinct margins (Fig. 2b). On histologic examination, predominant foamy histiocytes were observed in the mature lamellar bone, and these cells were well expressed on CD68 immunohistochemical staining (Fig. 2c, d). The diagnosis of JXG was confirmed. After 5 years and 8 months off treatment, the number of variable-sized skin lesions was increased, and the dorsal back lesion was resected. The pathology was also confirmed as JXG with foamy histiocytes (Fig. 4d). Brain MRI showed stable multiple skull lesions. There was no new lesion on abdominal ultrasound and WBBS.

Discussion

The term histiocyte encompasses two cell lines, monocyte-macrophages and specialized antigen-presenting dendritic cells. Histiocytic syndromes are rare disorders resulting from the proliferation of cells of both the monocyte-macrophage lineage and the Langerhans dendritic cell series. Histiocytoses represent a large, puzzling group of diseases whose classification continues to change [1, 9–11]. In 1987, the first classification of histiocytosis consisted of three categories: Langerhans cell, non-Langerhans cell-related, and malignant histiocytoses [3]. In the recent 2016 revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages, five groups were categorized based on clinical, radiological, pathological, genetic, and molecular features: Langerhans group (L group), cutaneous and mucocutaneous histiocytosis (C group), malignant histiocytoses (M group), Rosai-Dorfman disease and miscellaneous noncutaneous, non-Langerhans cell histiocytoses (R group), and hemophagocytic lymphohistiocytosis and macrophage activation syndrome (H group).

LCH is a disorder characterized by clonal proliferation of abnormal histiocytic cells that have the characteristics of Langerhans cells, and are classified into the L group [1]. This disorder has a wide age range from children to elderly. The incidence of this disorder is estimated to be about 4 or 5 per million per year in childhood, with a peak incidence from 1 to 5 years and a male predilection ranging from 1.5:1 to 3.7:1 [12, 13]. In children, the disease can be limited to a unifocal lesion in the bone, soft tissue, or skin, and multifocal lesions in the bone or lymph node, and occasionally it can extend to a multisystem disease that involves two or more organ systems. Pathologically, LCH expresses CD1a, langerin, and S100 protein, and it shows Birbeck granules on ultrastructural examination. Bone lesions are most likely to be confused with osteomyelitis, especially chronic recurrent multifocal culture-negative disease. LCH has few plasma cells

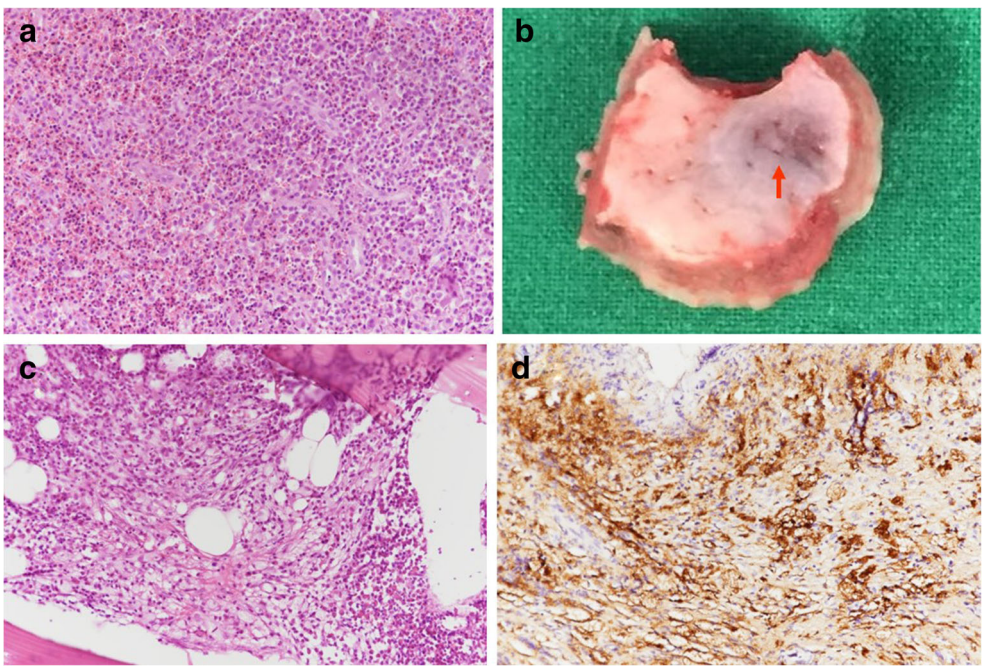

Fig. 2 The Langerhans cell histiocytosis and juvenile xanthogranuloma of the skull. **a** Pathologically, eosinophils were predominantly observed (original magnification ×200). **b**: Intraoperatively, the occipital skull lesion showed a focal osteolytic change with an indistinct margin (red arrow). **c** Pathologically, predominant foamy histiocytes were observed in the mature lamellar bone (original magnification ×200). **d** These cells were well expressed on CD68 immunohistochemical staining (original magnification ×200)

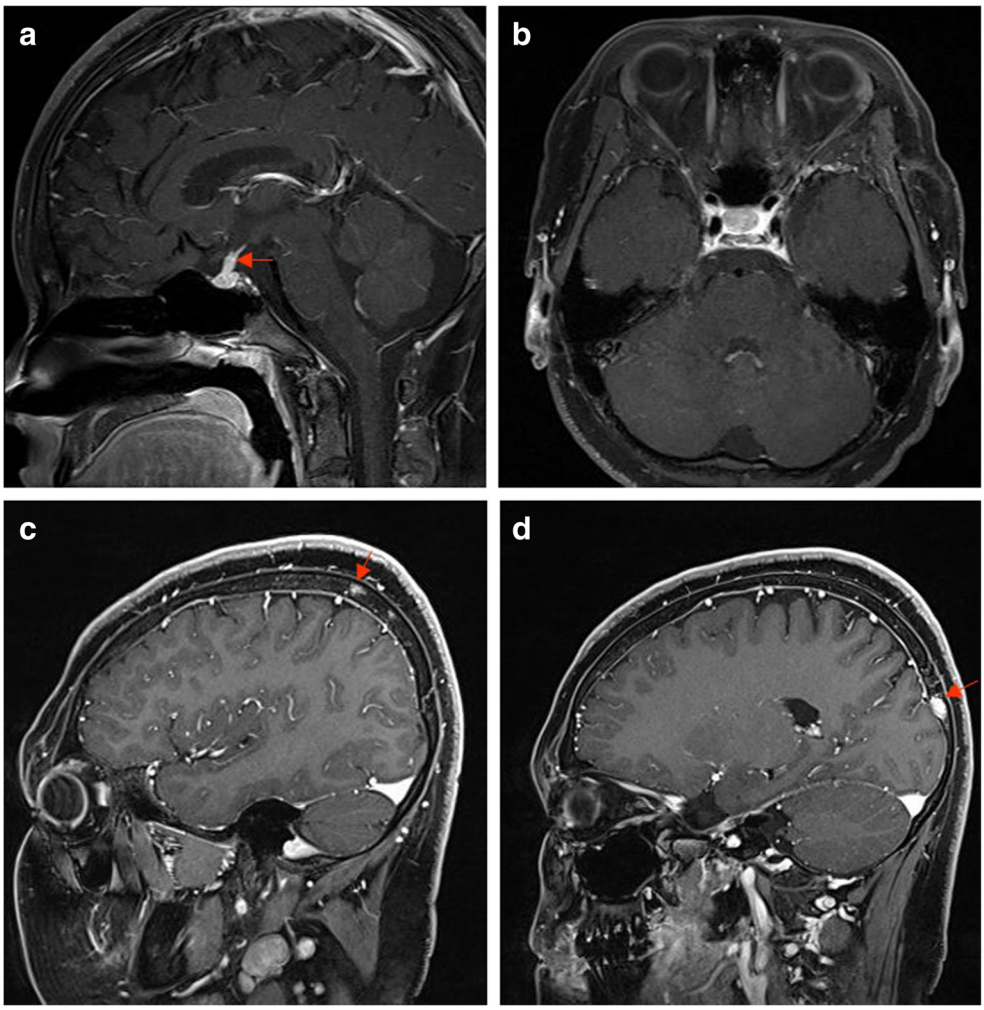

Fig. 3 The follow-up radiologic findings. **a** Brain MRI showed thickening of the pituitary stalk with enhancement (red arrow), suggestive of LCH involvement. **b** There was no recurrence in the sphenoid bone on brain MRI. **c** Brain MRI revealed an enhancing lesion in the left parietal bone (red arrow). **d** Brain MRI showed an enhancing lesion in the left occipital bone (red arrow)

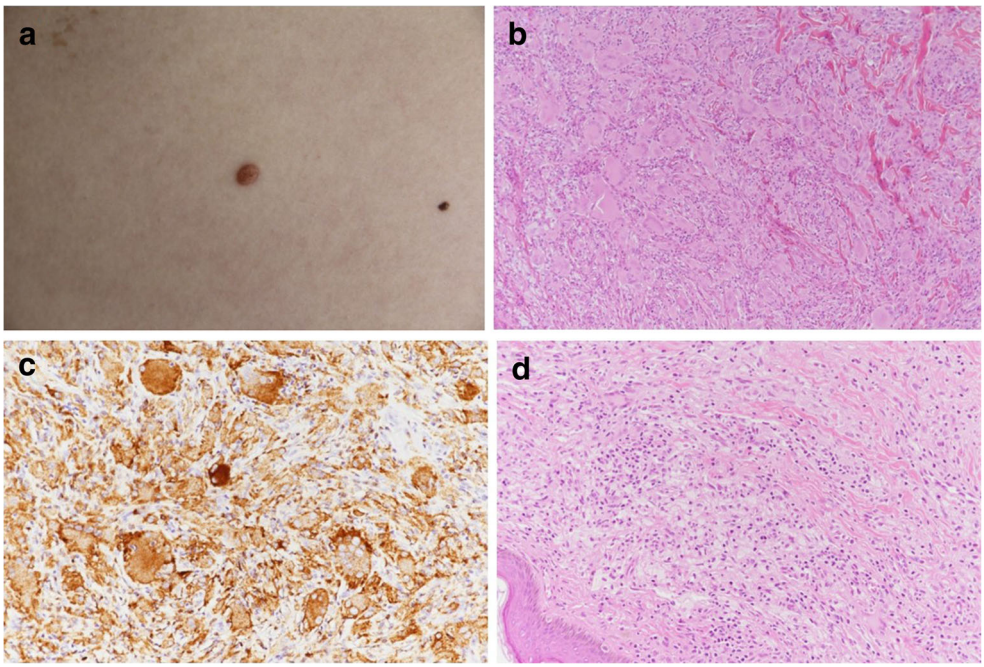

Fig. 4 The skin lesions of juvenile xanthogranuloma. **a** There were subcutaneous, asymptomatic, yellowish, and 0.6-cm-sized papules on the posterior neck lesion. **b** The pathology showed intradermal aggregation of Touton-type giant cells with foamy histiocyte infiltration (original magnification ×100). **c** The tumor cells were immune-positive for CD68 (original magnification ×200). **d** The pathology of the dorsal back lesion showed intradermal foamy histiocytes (original magnification ×200)

among LCH cells, but it may have more in the surrounding inflammatory reaction. Pituitary LCH must be distinguished from other tumorous conditions such as germ cell tumors. The prognosis is variable from self-healing to life-threatening disseminated lesions.

The non-LCH includes JXG, and JXG is classified into the C group [1]. The JXG family of lesions has many parallels to LCH. There are small solitary lesions, mostly cutaneous, but also larger and deep lesions that, like the skin lesions, are amenable to slow regression [14]. Skin lesions in JXG tender to disappear in most patients. Pathological findings show dermal nodular infiltrate of foamy histiocytic cells with features of Touton cells. These histiocytes are immune-positive for CD68 and factor XIIIa, and negative for S100 and CD1a. A small subpopulation of young children, mostly younger than 1 year, has a widespread systemic JXG with involvement of the skin, subcutaneous tissues, liver, spleen, lungs, bones, meninges, iris of the eye, and less commonly, the pituitary stalk of the brain. Rare overlap with LCH occurs in the same patient, concurrently or asynchronously, but JXG does not involve the lymph nodes [2, 5–8]. In its usual form, JXG is a benign dermal histiocytic disorder that occurs as single or multiple yellowish nodules that usually primarily involve the head and neck, trunk, or upper extremities [14–17]. They spontaneously resolve within several years. Rarely, the disorder may present systemically and can cause significant morbidity and occasionally death. Disseminated JXG is a rare systemic and clinically aggressive proliferation of histiocytes similar to that seen in dermal JXG.

Concomitant or metachronous co-existence of LCH and JXG has been reported in the same patients [2, 5–8]. These diseases have a clinical and histopathological similarity such as a common skin lesion, systemic involvement in some cases, prevalence in children, and possibility of spontaneous regression. Both etiologies are unclear. LCH has usually been considered a reactive or neoplastic lesion of Langerhans cell histiocytes [18]. However, JXG is generally considered as reactive lesion from monocyte-macrophage lineage [19]. Even if both are clinically and biologically distinct disorders, a close relationship could be suggested with clinical co-presentation in the same patients. Like this case, some patients who developed JXG following LCH treatment have been reported [5–8]. The time span ranged from months to years. The relationship between LCH and JXG is poorly understood. But, some authors hypothesized that the inflammatory reaction associated with LCH or under the influence of chemotherapy may precipitate the development of JXG [2, 7, 8]. The change in the local cytokine environment may activate macrophages [19]. The lesions of JXG following LCH and systemic therapy were located in the cutaneous and mucocutaneous areas such as the eyelid, axilla, throat, thigh, trunk, perianus, extremities, cheek, external auditory canal, and forehead [2, 5–8]. Interestingly, this case presents the disseminated form of JXG affecting the skin and skull.

Conclusion

We report a case of disseminated JXG occurring after treatment of LCH. These clinical co-presentations suggested a close relationship between their pathogenesis.

Acknowledgments This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Science, ICT, & Future Planning (2017R1A1A1A05001020).

Compliance with ethical standards

Conflict of interest The authors declare no potential conflict of interest related to this article.

References

1. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, Requena-Caballero L, Jordan MB, Abdel-Wahab O, Allen CE, Charlotte F, Diamond EL, Egeler RM, Fischer A, Herrera JG, Henter JI, Janku F, Merad M, Picarsic J, Rodriguez-Galindo C, Rollins BJ, Tazi A, Vassallo R, Weiss LM, Histiocyte S (2016) Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood 127(22):2672–2681. https://doi.org/10.1182/blood-2016-01-690636
2. Strehl JD, Stachel KD, Hartmann A, Agaimy A (2012) Juvenile xanthogranuloma developing after treatment of Langerhans cell histiocytosis: case report and literature review. Int J Clin Exp Pathol 5(7):720–725
3. Chu T, D'Angio GJ, Favara BE, Ladisch S, Nesbit M, Pritchard J (1987) Histiocytosis syndromes in children. Lancet 2(8549):41–42
4. Shani-Adir A, Chou P, Morgan E, Mancini AJ (2002) A child with both Langerhans and non-Langerhans cell histiocytosis. Pediatr Dermatol 19(5):419–422. https://doi.org/10.1046/j.1525-1470.2002.00118.x
5. Bains A, Parham DM (2011) Langerhans cell histiocytosis preceding the development of juvenile xanthogranuloma: a case and review of recent developments. Pediatr Dev Pathol 14(6):480–484. https://doi.org/10.2350/10-12-0950-CR.1
6. Perez-Gala S, Torrelo A, Colmenero I, Contra T, Madero L, Zambrano A (2006) Juvenile multiple xanthogranuloma in a patient with Langerhans cell histiocytosis. Actas Dermosifiliogr 97(9):594–598. https://doi.org/10.1016/S0001-7310(06)73474-3
7. Patrizi A, Neri I, Bianchi F, Guerrini V, Misciali C, Paone G, Burnelli R (2004) Langerhans cell histiocytosis and juvenile xanthogranuloma. Two case reports. Dermatology 209(1):57–61. https://doi.org/10.1159/000078589
8. Hoeger PH, Diaz C, Malone M, Pritchard J, Harper JI (2001) Juvenile xanthogranuloma as a sequel to Langerhans cell histiocytosis: a report of three cases. Clin Exp Dermatol 26(5):391–394. https://doi.org/10.1046/j.1365-2230.2001.00842.x
9. Lichtenstein L (1953) Histiocytosis X; integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schuller-Christian disease as related manifestations of a single nosologic entity. AMA Arch Pathol 56(1):84–102
10. Nezelof C, Basset F, Rousseau MF (1973) Histiocytosis X histogenetic arguments for a Langerhans cell origin. Biomedicine 18(5):365–371
11. Winkelmann RK (1981) Cutaneous syndromes of non-X histiocytosis. A review of the macrophage-histiocyte diseases of

the skin. Arch Dermatol 117(10):667–672. https://doi.org/10.1001/archderm.1981.01650100069034

12. Pileri SA, Grogan TM, Harris NL, Banks P, Campo E, Chan JK, Favera RD, Delsol G, De Wolf-Peeters C, Falini B, Gascoyne RD, Gaulard P, Gatter KC, Isaacson PG, Jaffe ES, Kluin P, Knowles DM, Mason DY, Mori S, Muller-Hermelink HK, Piris MA, Ralfkiaer E, Stein H, Su IJ, Warnke RA, Weiss LM (2002) Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 41(1):1–29. https://doi.org/10.1046/j.1365-2559.2002.01418.x
13. Salotti JA, Nanduri V, Pearce MS, Parker L, Lynn R, Windebank KP (2009) Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. Arch Dis Child 94(5):376–380. https://doi.org/10.1136/adc.2008.144527
14. Janssen D, Harms D (2005) Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the kiel pediatric tumor registry. Am J Surg Pathol 29(1):21–28. https://doi.org/10.1097/01.pas.0000147395.01229.06
15. Kaur MR, Brundler MA, Stevenson O, Moss C (2008) Disseminated clustered juvenile xanthogranuloma: an unusual morphological variant of a common condition. Clin Exp Dermatol 33(5):575–577. https://doi.org/10.1111/j.1365-2230.2008.02705.x
16. Weitzman S, Jaffe R (2005) Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. Pediatr Blood Cancer 45(3):256–264. https://doi.org/10.1002/pbc.20246
17. Zelger B, Cerio R, Orchard G, Wilson-Jones E (1994) Juvenile and adult xanthogranuloma. A histological and immunohistochemical comparison. Am J Surg Pathol 18(2):126–135. https://doi.org/10.1097/00000478-199402000-00002
18. Egeler RM, van Halteren AG, Hogendoorn PC, Laman JD, Leenen PJ (2010) Langerhans cell histiocytosis: fascinating dynamics of the dendritic cell-macrophage lineage. Immunol Rev 234(1):213–232. https://doi.org/10.1111/j.0105-2896.2009.00883.x
19. Zelger BW, Sidoroff A, Orchard G, Cerio R (1996) Non-Langerhans cell histiocytoses. A new unifying concept. Am J Dermatopathol 18(5):490–504. https://doi.org/10.1097/00000372-199610000-00008